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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,487	03/26/2001	Susanne Dagmar Pippig	4-31193A	9170

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EXAMINER
LI, RUIXIANG

ART UNIT	PAPER NUMBER
1646	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/817,487	PIPPIG ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-21 and 23-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-21 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 and 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicants' election with traverse of Group I (Claims 1-12, 14-21, 23, and 24) and the species mMuSK-RII in Paper No. 11 filed on 08/13/2002 is acknowledged. The traverse is on the ground that the species recited in Claims 2-5 are all mutant MuSK Receptors. In view of applicants' clarification and argument, species election requirement has been withdrawn.
2. Applicants' amendment in Paper No. 11 filed on 08/13/2002 has been entered in full. Claims 13 and 22 have been canceled. Claims 2 and 5 have been amended. New claims 25 and 26 have been added. Thus, Claims 1-12, 14-21, and 23-26 are pending and under consideration.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional applications, 60/266,331 filed on March 30, 2000.

Drawings

4. The drawings filed on 03/26/2001 are objected by the Examiner because of the defect, as detailed in the attached PTO-948.

A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Information Disclosure Statement

5. The information disclosure statement filed August 2, 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. The information of *references on sequence data* from Databases is incomplete. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that *a new PTO-1449 form be submitted for the application* and that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections—35 USC § 112, 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 15 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying genetically modified cells comprising introducing a population of mammalian cells both a heterologous DNA sequence encoding a protein of interest and a nucleic acid sequence encoding the mMuSK-R on the same vector, does not reasonably provide enablement for a method of identifying genetically modified cells comprising introducing a population of

mammalian cells a heterologous DNA sequence encoding a protein of interest and a nucleic acid sequence encoding the mMuSK-R which are on different vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim.

The factors considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 15 and 21 are drawn to a method of identifying genetically modified cells comprising introducing a population of mammalian cells both a heterologous DNA sequence encoding a protein of interest and a nucleic acid sequence encoding the mMuSK-R. It is well known in the art that expression of a heterologous DNA sequence can be indicative for another if two heterologous DNA sequences are on the same vector (*IDS*, *J. Cell Biology* 146:1133-1146, 1999; Persons et al, *Blood* 90:1777-1786, 1997). However, the state of the art is such that it is unpredictable whether expression of a cDNA can be indicative for another cDNA if they are on different vectors, due to the nature of complexity of expressing a heterologous DNA. The instant disclosure fails to provide working examples, sufficient guidance, or information on how to make certain that a heterologous DNA sequence encoding a

protein of interest and a nucleic acid sequence encoding the mMuSK-R, which are introduced a population of mammalian cells on different vectors, will always be expressed at same time. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed broad invention embraced by the instant claims.

Claim Rejections—35 USC § 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-12, 14-21, and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12, 14-21, and 23-26 are indefinite because method steps do not necessarily achieve the goal set forth in the preamble of the claims. Only cells which are modified to express mMuSK-R would be identified by carrying out the method steps, whereas cells which are genetically modified by mutations or transformation with other DNA would not be identified.

Claim Rejections—35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-4, 6-8, 10-12, and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhou et al. (*IDS, J. Cell Biology* 146:1133-1146, September 6, 1999).

Zhou et al. teach a method of identifying genetically modified mouse myogenic cells expressing various mutated muscle specific tyrosine kinase receptors (mMuSK-Rs). Zhou et al. teach an expression vector encoding a rat MuSK-rat trkC chimera. the cDNA was expressed under the control of the Rous Sarcoma virus long terminal repeat (bottom of left column, page 1134). In this chimera, the cytoplasmic domain was fused to the cytoplasmic domain of rat trkC. The cytoplasmic domain or intracellular domain (amino acid residues 516-869) of the rat MuSK-R, which includes the catalytic site (amino acid residues 672-691), was deleted. The retrovirus expression vector was introduced into mammalian cells, a mouse myogenic line (See Cell Culture at page 1134). The transfection of cells with the virus vector was followed by the selection process, which would separate the genetically modified cells from the non-modified cells (See Cell Culture at page 1134).

Zhou et al. further teach identifying cells expressing the rat MuSK-rat trkC chimera protein and other various rat mMuSK-Rs using an antibody which specifically binds to MuSK-R (See under Immunohistiochemistry at page 1134). These various rat mMuSK-Rs can be also considered as mMuSK-Rs set forth in SEQ ID NO:2 because both rat MuSK-R and human MuSK-R have 869 amino acid residues and share 93.9% overall sequence homology (See attached sequence alignment).

Thus, the reference of Zhou et al. meets the limitations of Claims 1-4, 6-8, 10-12, and 21.

Claim Rejections—35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 9, 14-17, 19-20, 23, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bordignon et al. (*IDS*, WO 95/06723, March 9, 1995) in view of Zhou et al. (*IDS*, *J. Cell Biology* 146:1133-1146, September 6, 1999).

Bordignon et al. teach a method that clearly includes all the steps recited in the claims except the use of a cell surface mMuSK-R as an identification marker for the genetically modified mammalian cells (See, e.g., Claims 1 and 7-9; 2nd paragraph of page 4).

Zhou et al. teach a method of identifying genetically modified mouse myogenic cells expressing various mutated muscle specific tyrosine kinase receptors (mMuSK-Rs). Zhou et al. teach an expression vector encoding a rat MuSK-rat trkC chimera. the cDNA was expressed under the control of the Rous Sarcoma virus long terminal repeat (bottom of left column, page 1134). In this chimera, the cytoplasmic domain was fused to the cytoplasmic domain of rat trkC. The cytoplasmic domain or intracellular domain (amino acid residues 516-869) of the rat MuSK-R, which includes the catalytic site (amino acid residues 672-691), was deleted. The retrovirus expression vector was introduced into mammalian cells, a mouse myogenic line (See Cell Culture at page 1134). The transfection of cells with the virus vector was

followed by the selection process, which would separate the genetically modified cells from the non-modified cells (See Cell Culture at page 1134).

Zhou et al. further teach identifying cells expressing the rat MuSK-rat trkC chimera protein and other various rat mMuSK-Rs using an antibody which specifically binds to MuSK-R (See under Immunohistiochemistry at page 1134). Because Mu-SK-Rs from human and rats share a very high degree (93.9%) over all amino acid sequence homology (See attached sequence alignment) and the anibody recited by the instant claim were prepared using an epitope in the extracellular domain of human Mu-SK-Rs, it is reasonable to assume that the antibodies used by Zhou et al. bind specifically to the epitope recognized by the antibody H1.

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made, as an alternative approach, to use the expression of mMuSK-Rs for identifying the genetically modified hematopoietic cells or for the immunoselection of transduced mammalian cells with a reasonable expectation of success. One would have been motivated to do so because (i) the general teaching by Bordignon et al. on the use of a mutated cell surface receptor for identifying the genetically modified mammalian cells or for the immunoselection of transduced mammalian cells and (ii) the successful use of a cell surface mMuSK-R as a identification marker for identifying genetically modified mouse myogenic cells, as demonstrated by Zhou et al.

14. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bordignon et al. (WO 95/06723, March 9, 1995) in view of Zhou et al. (*IDS, J. Cell Biology* 146:1133-1146, September 6, 1999), as applied to Claims 9, 14-17, 19-20, and 23

above, and further in view of either Persons et al. (*IDS, Blood* 90:1777-1786, 1997) or Hildinger et al. (*IDS, Gene Therapy* 6:1222-1230, 1999).

Bordignon et al. teach a method of identifying genetically modified mammalian cells (including human hematopoietic cells) and a method for the immunoselection of transduced cells, and Zhou et al. teach a method of identifying genetically modified mouse myogenic cells expressing various mMuSK-R, as applied to Claims 9, 14-17, 19-20, and 23 above. Neither Bordignon et al. nor Zhou et al. teach the use of the retroviral vector recited in the claim.

Persons et al. teach the use of a bicistronic murine stem cell virus, MSCV (Abstract). Hildinger et al. teach the use of bicistronic retroviral vectors, MESV, SFFV, MoMLV (See, e.g., Fig.1).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made, as an alternative approach, to use the retroviral vectors taught by Persons et al. or Hildinger et al. for the expression of mMuSK-Rs for identifying the genetically modified hematopoietic cells or for the immunoselection of transduced mammalian cells with a reasonable expectation of success. One would have been motivated to do so because both Persons et al. and Hildinger et al. have demonstrated the high efficiency of expression systems using these retroviral vectors.

Claim Objections—Minor Informalities

15. Claims 18-20 are objected to because each claim appears to depend from Claim 17 not Claim 16. Appropriate correction is required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

Ruixiang Li
Examiner
August 24, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER